

**REMARKS: CLAIM REJECTION UNDER 35 U.S.C. § 103(a)**

Claims 1-8 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement; and claims 9, 10, 12 and 13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gidlund U.S. Patent No. 6,436,449 (“Gidlund”). Accordingly, Applicant respectfully submits the following.

**Rejections Under 35 U.S.C. §112**

Applicant respectfully submits that the phrase “less than 0.1 ml per kg of body weight of a patient” finds adequate support in the specification as filed and thus does not add new matter. The specification indicates that selective inhibition of COX-2 relative to COX-1 was observed in research and indicated that at a solution of 2.3 percent of *Morinda citrifolia* juice inhibited COX-2 by 60% while the inhibition of COX-1 was only 20 percent. Thus, the specification indicates that *Morinda citrifolia* juice shows selective COX-2 inhibition only when administered at very low dosages.

Specifically, the limitation of the maximum dosage of 0.1 ml per kg of body weight of a patient finds support in the specification at page 15, line 1 to page 15, line 7. The specification indicates that “biochemical assay results show that a concentration of 2.3 percent inhibition of COX-1 enzyme is four times less than inhibition of the COX-2 enzyme. Alternatively, this demonstrates COX-2 is inhibited to four times the extent as COX-1. Specifically, the results show that inhibition of COX-1 was 20 percent while inhibition of COX-2 was almost 60 percent. When the concentration was increased to 10 percent, the inhibition of COX-1 is shown to be approximately 83 percent while the inhibition of COX-2 is approximately 84 percent.” Accordingly, the Applicant’s originally filed specification supports “the surprising result that in

some circumstances less “*Morinda citrifolia* juice provides more [selective] inhibition...”  
Specification, page 15.

Applicant’s disclosure shows that COX-2 selectivity is undermined by excessive, increased concentrations. Accordingly, the specification provides support for limiting the maximum dosage provided to a patient in a given period of time in a effort to maintain selective COX-2 inhibition. If a patient were given excessive doses of *Morinda citrifolia* in a given period of time the selective COX-2 inhibition of the administration would be undermined.

#### Rejections Under 35 U.S.C. §103

Applicant respectfully submits that Gidlund fails to teach the claim limitations cited in the present application because: 1) Gidlund does not teach administering low doses that produce selective COX-2 inhibition; and 2) Gidlund teaches a method for treating tinnitus not method for treating pain through selective COX-2 inhibition.

#### 1. Gidlund Does Not Teach a Method for Reducing Pain By Selective COX-2 Inhibition.

The difference between treatment of pain and selective COX-2 inhibition is patentable. COX-2 expression is associated with pain and inflammation. COX-1 is a constitutively active enzyme responsible for maintaining the mucosal living of the stomach. When COX-2 is inhibited, pain is reduced. When COX-1 is inhibited, patients experience uncomfortable side effects, including gastric ulcers.

Compounds or formulations, which favorably influencing pain, do not have a reasonable probability for reducing pain by selective COX-2 inhibition. For example, a popular treatment of chronic pain and inflammation involves the use of non-steroidal anti-inflammatory drugs

(NSAIDs). NSAIDs inhibit both COX-2 and COX-1. While NSAIDs have been effective in reducing inflammation and pain, NSAIDs have a number of adverse side effects. The major side effects of NSAIDs are gastrointestinal related. In order to provide relief pain associated with COX-2 without inhibiting COX-1, drug companies have attempted to produce selective COX-2 inhibitors (e.g., VIOXX).

Applicant's claims contain limitations which require that the juice be administered in small dosages in order to limit undesired COX-1 inhibition. Applicants' disclosure demonstrates the importance and non-obviousness of administering the appropriate concentration of *Morinda citrifolia*. In particular, Applicants' experiments provide the non-obvious discovery that at some concentrations, selective COX-2 inhibition was achieved, and at other concentrations it was not. Specification, pg. 15. The Applicants indicated, "[t]he data suggests the surprising result that in some circumstances 'less' *Morinda citrifolia* juice provides 'more' inhibition selectivity." Specification, pg. 15. Applicants' disclosure shows that COX-2 selectivity is undermined by excessive, increased concentrations. Specification, pg. 15. It is only after the inherent COX-1 inhibiting qualities of *Morinda citrifolia* are limited by the methods of the present invention that selective COX-2 inhibition occurs.

2. Gidlund Teaches Administration of Excessive Dosages Which Do Not Produce COX-2 Inhibition.

It is desirable to produce a COX-2 inhibitor which is selective and allows the constitutively active COX-1 enzyme to maintain the mucosal lining in the stomach. These results suggest that limiting undesirable COX-1 inhibition by *Morinda citrifolia* juice may be accomplished only by appropriately limiting the concentration administered. Because Gidlund

teaches the administration of a quantity of juice that is higher than the amount necessary to achieve said selective COX-2 inhibition, the disclosure in Gidlund fails to read on the claims of the present invention.

The independent claims of the present invention include a limitation on the total amount of juice administered daily. Because Gidlund teaches that “the liquid extract from the *Morinda citrifolia* will be present in the medicament in the amount such as to provide a daily dosage of 0.1-2 ml, or 0.2-1 ml, e.g., 0.4-0.7 ml, per kg body weight of the patient,” Gidlund fails to teach every claimed limitation of the present invention. Gidlund provides specific instructions in column 5, lines 16-19 that any liquid extract would be administered through patient at a minimum dosage of .1 ml per kg of body weight of a patient. Accordingly, a 70 kg patient would be administered 7 ml of liquid extract from *Morinda citrifolia* each day.

As described in example 1 of the specification of the present application, the dosaging of *Morinda citrifolia* juice is critical to achieving selective COX-2 inhibition. If an excessive amount of juice is administered, the selective COX-2 properties of the *Morinda citrifolia* juice are diminished. In particular, page 15 of the specification indicates that,

Biochemical Assays show that a concentration of 2.31% produced an inhibition of COX- 2 which was 20%, while the inhibition of COX-1 was 10%, while the inhibition of COX- 2 was 60%. This is compared with the administration of 11% solution of *Morinda citrifolia* juice which produced an 83% inhibition of COX-1 and an 84% inhibition of COX-2. Accordingly, at greater concentrations, the selective COX-2 inhibition produced by the consumption of *Morinda citrifolia* products is limited.

Accordingly, COX-2 selective inhibition with *Morinda citrifolia* juice is sensitive or related to the concentration administered. Excessive concentration of *Morinda citrifolia* juice reduced the selective COX-2 inhibition properties of the administration. Accordingly, the administration disclosed by Gidlund which may be effective for inhibiting COX-2 and COX-1,